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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,410	03/01/2004	Robert L. Martuza	066683-0198	4953

22428 7590 03/30/2010

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
03/30/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/788,410	**Applicant(s)** MARTUZA ET AL.	
	Examiner WU-CHENG Winston SHEN	**Art Unit** 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 March 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *16,18-20 and 28-32*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 01/25/2010
13. ☐ Other: _____.

Continuation of 11. does NOT place the application in condition for allowance because:

(I) Applicant's arguments have failed to overcome claims 16, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of Vile et al. (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. Ann Oncol. 5 Suppl 4:59-65, 1994). Applicant's arguments filed After-Final on 03/12/2010 have been fully considered and they are not persuasive. Previous rejection is maintained for the reasons of record advanced on pages 2-17 of the Final office action mailed on 11/12/2009.

(i) Applicant argues that the post-interview final Office Action, dated November 12, 2009, in no way reflects Examiner Shen's position during the interview. Instead, the examiner now asserts out of the context of the interview: (i) that the efficacy of the claimed HSV in cancer therapy is the "intended use" and therefore is not given patentable weight because the present claims are product claims, (ii) that "eliciting an immune response" is considered an "inherent" property of the cytokine, and (iii) that the HSV strains mentioned in Rabkin Declaration are "not commensurate in scope with the claimed HSV."

In response, the Examiner notes that the Final office action mailed on was made after careful review of Applicant's official arguments filed on 07/20/2009, which was filed after the interview held on 07/14/2009. Applicant's exhibits and written arguments filed on 07/20/2009 were certainly not presented during the interview held on 07/09/2009, which explains why the Final office action is "out of the context of the interview". Nevertheless, the asserted "out of the context of the interview" issues (i)-(iii) had been previously raised by Applicant and responded by Examiner (See e.g. pages 12-13 of the office action mailed on 08/18/2008 and pages 8-14 of the office action mailed on 03/18/2009) before the latest Final office action mailed 11/12/2009. The Examiner's position has been consistent throughout the prosecution, which is further elaborated in this advisory action.

The following statements had been documented in interview summary mailed on 07/14/2009: "The Examiners encourage Applicants to provide evidence(s) supporting that expression of a cytokine gene from a HSV indeed blocks the HSV replication because, in the reference cited in filed Declaration, the cytokine is not expressed from a HSV, which is distinct from cytokine expressed from a HSV as claimed. It appears that the precise time point when the cytokine gene is expressed from HSV (e.g. early gene versus late gene expression) would affect the role of expressed cytokine: either (i) preventing HSV replication and thereby preventing oncolytic activity of HSV as Applicant argues or (ii) enhancing oncolytic activity of HSV as taught by Vile et al. Secondly, the Examiners encourage Applicants to provide evidences if unexpected results (e.g. synergistic effect in killing tumor cells when a cytokine gene is expressed from claimed HSV) have been observed".

It is worth noting that submission of arguments/exhibits by Applicant does not automatically lead to the conclusion that arguments/exhibits are persuasive, which Applicant appears to assert.

(ii) Applicant argues that the examiner improperly invoked "intended use" to substantiate the rejection. Applicant asserts that the combination of the claimed oncolytic HSV vector with the recited cytokine expression should be given full weight as a patentable distinction over prior-art teachings because such combination was not suggested by the prior art. Applicant states that applicants have made declaration evidence of record to the effect that, at the filing time, conventional wisdom actually directed one of ordinary skill away from the notion of expressing cytokines in an oncolytic vector, such as the recited HSV vector; this is, because certain cytokines were reported to protect the host from HSV infection, which is prerequisite to the operation of an oncolytic vector. Applicant states that the examiner's discounting of presently recited structural (i.e., genomic) features on the grounds of "intended use" is improper.

In response, Applicant continues to assert that "conventional wisdom" directed one of ordinary skill away from the notion of expressing cytokines in an oncolytic vector, such as the recited HSV vector; this is, because certain cytokines were reported to protect the host from HSV infection. The Examiner notes that, throughout the prosecution, Applicant has never provided any evidence addressing the key issue regarding precise time point when the cytokine gene is expressed from HSV (e.g. early gene versus late gene expression), which would affect the role of expressed cytokine: either (i) preventing HSV replication and thereby preventing oncolytic activity of HSV as Applicant argues or (ii) enhancing oncolytic activity of HSV as taught by Vile et al. (see e.g. pages 7-8 of Applicant's arguments filed on 12/18/2008). As a related issue, the claimed structural (i.e., genomic) features "HSV with a null mutation in the gamma34.5 gene" is clearly taught by Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001). The "intended use" issue is only relevant to "a cytokine gene" cloned in the HSV vector with a null mutation in the gamma34.5 gene. This issue had been clearly responded on pages 13-14 of the Non-Final office action mailed on 03/18/2009. It is worth noting that independent claim 16 does not require cytokine gene been expressed from any specific location within the genome of claimed HSV. In other words, claim 16 only requires a simple sub-cloning of a cytokine gene taught by Vile from a plasmid to the HSV with a null mutation in the gamma34.5 gene" taught by Roizman et al.

(iii) Applicant argues that the property of the cytokine must be evaluated in the viral context. Applicant states that Vile describes: (i) transduction of tumor cells in vitro with cDNA encoding a cytokine and then returning the cells in vivo to animal tumor models; and (ii) direct injection of naked DNA encoding cytokine genes under a Tyr-promoter. See abstract, page 61, left column, and page 63, right column. Neither embodiment teaches or suggests that expressing a cytokine in the context of an oncolytic virus can achieve cancer therapy effects by eliciting an immune response against cancer cells.

In response, please see response in (ii) above. Moreover, the Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc. that forecloses the argument that a specific teaching, suggestion, or

motivation is an absolute requirement to support a finding of obviousness. See recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc., the suggestion and motivation to combine Roizman et al. and Vile et al. has been clearly set forth above in this office action mailed on 11/12/2009. In this regard, it is worth reiterating that one having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. with the teachings of Vile et al. (1994) because (i) the gamma34.5 gene mutation would result in a non-pathogenic vector, as taught by Roizman et al. (See last paragraph, column 5), and (ii) the exogenous expression of a cytokine gene would result in diminishing or eliminating tumorigenicity of tumor cells, as taught by Vile et al.

It is furthermore noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

(iv) Applicant asserts that the vectors used in cited publications are commensurate in scope with the claimed invention. Applicant states that all these publications were submitted in support of the notion that expression of a cytokine resulted in prevention or decreased HSV replication, which is required for the claimed invention. Specifically, Exhibit A shows that IFN-gamma2 and IFN-beta block HSV-1 replication; Exhibit C confirms that TNF and IFNgamma have antiviral activities against HSV-1 and HSV-2; Exhibit F discloses that IFN-gamma B/D is highly effective in preventing viral replication and cell destruction induced by HSV-1; Exhibit H presents that IL-3 markedly inhibits HSV-1 replication in primary mouse embryonic head cell cultures; and Exhibit 1 demonstrates that expression of IL-2 results in decreased HSV-1 replication in vivo and in vitro. Applicant states that the examiner disregarded the fact that all viruses used by these references fall into the same category of HSV vectors delineated by the claims, but emphasized that the specific genetic mutations are not exactly the same in the references.

In response, throughout the persecution, it is crystal clear that the specific "gamma34.5 mutation", which renders the HSV non-pathogenic and virus cannot replicate and spread, is the MOST CRITICAL element of claimed products. As an example, claim 16 filed on 09/07/2004 reads as follows: A herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a desired protein and (ii) an alteration, relative to wild type, in the gamma34.5 gene. Therefore, the Examiner maintains the position that none of declaratory evidence provided in Exhibits A, C, F, and H that accompany the Rabkin Declaration is commensurate in scope with the claimed HSV products --- i.e. a HSV with null mutation of both gamma34.5 (recited in independent claim 16) and ribonucleotide reductase (recited in dependent claim 19) and a cytokine gene inserted in the HSV genome.

(v) Applicant assets that the unexpected therapeutic effects achieved by the claimed HSV is left unchallenged. Applicant states that the examiner asserts that Vile demonstrates tumorigenicity as cDNAs encoding cytokines were detected in vivo. See final Office Action, page 14, first full paragraph. In fact, one skilled in the art would not have drawn the same conclusion from Vile. Vile clearly shows that, although some degree of reduced mRNA is detected by RT-PCR, there is no indication of actual tumor reduction (page 62, right column), possibly leading to significant clinical results. Applicant states that Vile's protocol of returning tumor cells in vivo following transduction by a cytokine cDNA or injecting naked DNA encoding a cytokine in no way predicts the therapeutic outcome of the claimed invention, which entails the combination of an oncolytic HSV vector and expression of a cytokine.

In response, the Examiner had clearly addressed this issue in the non-Final office action mailed on 03/18/2009 (See page 12 and bridging paragraph pages 13-14 of office action mailed on 03/18/2009), which is reiterated below for clarity of this advisory action.

"Applicant argues that the prospect of combining the prior-art teachings invoked by the Examiner would have presented the skilled artisan with several scenarios, each fraught with a priori uncertainty:

(A) The expression or secretion of the cytokine could induce an anti-HSV immune response, which threatens the elimination of HSV-infected tumor cells before the HSV replicates and spreads. The oncolytic effect of HSV would be lost as a consequence, and the immune effect would be equivalent to that of a cytokine gene therapy approach where immunization against tumor antigens is intended.

(B) The replication of HSV, leading to apoptosis and/or cell lysis, is rapid enough to parallel an anti-HSV response that the cytokine induces. Accordingly, the virus still is able to spread and, while it alerts the immune system to viral antigens, it also induces an anti-
tumor immune response.

(C) The replication of HSV leads to apoptosis or cell lysis before the release of a sufficient amount of expressed cytokine, thereby realizing benefit from oncolytic therapy only.

Which of these scenarios might prevail was entirely unpredictable, in view of contemporaneous state of the art. Applicant argues that this lack of predictability also is sufficient unto itself to defeat the notion that the claimed HSV is obvious within the meaning of Section 103" (See page 12 of office action mailed on 03/18/2009).

"The Examiner acknowledges that the intended use for cancer gene therapy of the HSV recited in the claims of instant application may function in multiple possible scenarios, including (A) to (C) discussed by Applicant. The Examiner also acknowledges that even as of current status of art, the outcome of cancer gene therapy in general remains unpredictable and needs to be evaluated on a case-by-case basis. However, it is worth emphasizing, again, the claims of instant application is directed to a product, not a method of using said product in cancer gene therapy that results a statistically significant reduction in tumor growth, as Applicant argues. In this regard, as stated in the response under (i) section, claim 16 is a product claim, a HSV with null mutation of both gamma34.5 and a cytokine gene inserted in the HSV genome. The structure and inherent properties of the structure of claimed HSV as a whole was clearly prima facie obvious based on the combined teachings of Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001) in view of Vile et al. (Ann Oncol. 5 Suppl 4:59-65, 1994). The efficacy of the claimed HSV in cancer gene therapy is the intended use of the claimed HSV, which the Examiner agree with Applicant that the intended use of the claimed HSV in treating a given cancer remains unpredictable as Applicant argues that several possible scenarios may occur. Nevertheless, a skilled person in the art would be motivated to make the claimed HSV based on the

combined references and to test how effective the claimed HSV may be in cancer gene therapy" (See bridging paragraph pages 13-14 of office action mailed on 03/18/2009).

It is worth noting again that independent claim 16 does not require cytokine gene been expressed from any specific location within the genome of claimed HSV vector. In other words, claim 16 only requires a simple sub-cloning of a cytokine gene taught by Vile from a plasmid to the "HSV with a null mutation in the gamma34.5 gene" taught by Roizman et al. Furthermore, as stated in this advisory action and in interview summary mailed on 07/14/2009, throughout the prosecution, Applicant has never provided any evidence addressing the key issue regarding precise time point when the cytokine gene is expressed from HSV (e.g. early gene versus late gene expression), which would affect the role of expressed cytokine: either (i) preventing HSV replication and thereby preventing oncolytic activity of HSV as Applicant argues or (ii) enhancing oncolytic activity of HSV as taught by Vile et al.

(II) Applicant's arguments have failed to overcome the rejection of claims 18-20 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of Vile et al. (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. Ann Oncol. 5 Suppl 4:59-65, 1994) as applied to claims 16, 28, and 29 above, and further in view of Chang et al. (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, Virology, 185(1):437-40, 1991). Applicant's arguments filed After-Final on 03/12/2010 have been fully considered and they are not persuasive. Previous rejection is maintained for the reasons of record advanced on pages 17-21 of the Final office action mailed on 11/12/2009.

Applicant's Arguments and Responses to Applicant's Arguments are the same as discussed in the preceding rejection of claims 16, 28, and 29 as being unpatentable over Roizman et al. in view of Vile et al. Furthermore, regarding the motivation to combine the cited reference, it is worth adding that, bearing the goal of targeting specifically to cancer cells taught by Roizman et al. and Vile et al., Chang et al. teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells (e.g. cancer cells), but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991). Chang et al. further teaches that the introduction of a foreign gene (e.g. a cytokine gene taught by Vile et al.) into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991).

(III) Applicant's arguments have failed to overcome the rejection of claim 30-32 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of Vile et al. (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. Ann Oncol. 5 Suppl 4:59-65, 1994) as applied to claim 16, 28, and 29 above, and further in view of McKay et al. (WO 92/14821, publication date 09/03/1992, PCT/US92/01375, priority date 02/22/1991), and Wright, Jr. (US 5,639,656, issued Jun. 17, 1997, filed 03/31/1994).. Applicant's arguments filed After-Final on 03/12/2010 have been fully considered and they are not persuasive. Previous rejection is maintained for the reasons of record advanced on pages 21-25 of the Final office action mailed on 11/12/2009.

Applicant's Arguments and Responses to Applicant's Arguments are the same as discussed in the preceding rejection of claims 16, 28, and 29 as being unpatentable over Roizman et al. in view of Vile et al.

/Wu-Cheng Winston Shen/
Primary Examiner, Art Unit 1632